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Pharmaceutical supply chain models: A synthesis from a systems view of operations research

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ABSTRACT

This research evaluates reconfiguration opportunities in Pharmaceutical Supply Chains (PSC) resulting from technology interventions in manufacturing, and new, more patient-centric delivery models. A critical synthesis of the academic and practice literature is used to identify, conceptualise, analyse and categorise PSC models. From a theoretical perspective, a systems view of operations research is adopted to provide insights on a broader range of OR activities, from conceptual to mathematical modelling and model solving, up to implementation.

The research demonstrates that: 1) current definitions of the PSC are largely production-centric and fail to capture patient consumption, and hence healthcare outcomes; 2) most PSC mathematical models lack adequate conceptualisation of the structure and behaviour of the supply chain, and the boundary conditions that need to be considered for a given problem; 3) models do not adequately specify current unit operations or future production technology options, and are therefore unable to address the critical questions around alternative product or process technologies; 4) economic evaluations are limited to direct costing, rather than systemic approaches such as supply chain costing and total cost of ownership.

While current models of the PSC may help with the optimisation of specific unit operations, their theoretical benefits could be offset by the dynamics of complex upstream (supply) and downstream (distribution and healthcare delivery) systems. To overcome these limitations, this research provides initial directions towards an integrated systems approach to PSC modelling. This perspective involves problem conceptualisation and boundary definition; design, formulation and solution of mathematical models, through to practical implementation of identified solutions. For both academics and practitioners, research findings suggest a systems approach to PSC modelling can provide improved conceptualisation and evaluation of alternative technologies, and supply network configuration options.

1. Introduction

With access to essential medicine being one of the building blocks of healthcare systems [1], policy measures aimed at reducing healthcare spending growth at the international level have targeted primarily the pharmaceutical industry, over the past decade [2]. In the UK, the healthcare system ranks higher for spending than for health outcomes [3], and pharmaceutical products have contributed to the lower end of manufacturing gross value added growth since 2010 [4,5]. At the same time, traditional pharmaceutical manufacturing is being challenged by emerging requirements, such as greater drug product personalisation, more participative healthcare enabled by the adoption of digital information and communication technology [6], and by the advancement of innovative technology interventions such as continuous manufacturing, which promise to achieve smaller footprints and greater responsiveness [7,8].

While these challenges have received greater attention in the mainstream business and engineering literature, it is still open to discussion whether, and to which extent, current approaches to PSC modelling adequately reflect and address such challenges. Research is now paying greater attention to the interdependences between Pharmaceutical Supply Chains (PSC) and the broader healthcare bundle [9]. Coordination between actors, and inventory management are still perceived to be the primary challenges in strengthening global health pharmaceutical delivery, however, the deployment of sophisticated inventory models is deemed insufficient per se to improve the current situation [10]. Novel approaches must be deployed to achieve greater “end-to-end” integration along the PSC through technology advances in medicines manufacturing and more patient-centric delivery models [7].

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The research presented in this paper aims to *inform* the debate on how to evaluate the multifaceted aspects of PSC reconfiguration opportunities enabled by technology interventions in medicine manufacturing, as well as more patient-centric delivery models. To do so it provides a critical synthesis of the state-of-the-art approaches commonly employed in the academic literature and industry practice to identify the relevant aspects of a PSC; to conceptualise those aspects through visualisation; and to quantitatively evaluate them. The following research questions are therefore addressed:

(1) "What is meant by PSC for modelling purposes?" (definition);
(2) "How is a PSC conceptualised through visualisation?" (conceptual models);
(3) "Which aspects of a PSC are expressed quantitatively, and how"? (mathematical models).

Gaps are identified by comparing and contrasting the characteristics of a PSC, which are currently modelled, with those that should be considered in a context where reconfigurations opportunities are being targeted, such as in [8].

The scope of this paper does not aim to include any type of models outlined to investigate a PSC. Models may be used, among other things, to rank multiple decision-making criteria, or establish statistical relationships between constructs as, for example, in surveys [11]. In line with the theoretical viewpoint taken by Carter et al. [12] it is, therefore, useful to distinguish between models for the advancement of theory building in supply chain *management* and models that contribute to the advancement of theory building in what is purportedly managed—the supply chain itself. The latter is the focus of this paper.

The paper is structured as follows. Section 2 sets out the terminology, materials, and methods. In Section 3 synthesising arguments are derived from the analysis of the literature to characterise archetypal PSC models. Theoretical and practical implications of each archetype are discussed in Section 4. Section 5 provides concluding remarks, and directions for future research.

2. Materials and methods

The rationale of a synthesis process is to achieve of a coherent conceptual structure of a topic, using the extant literature as the object of scrutiny [13,14]. The terminology, theoretical lenses, methods and materials relevant to this research are specified in the following sub-sections.

2.1. Basic terminology

As the focus of this research is modelling, it is necessary to define what is meant by a 'model' in this context.

In such fields as Operations Research (OR) how the analyst constructs a mental image of a problematic situation is often neglected. The analyst develops such an image by an *act of appreciation* from unorganised perceptions acquired through observation, and proceeds from such an image to formally represent the situation in symbolic terms [15]. Making reference to industrial systems Forrester [16] points out that models represent only what the analyst *believes* to be the nature of the system being studied, and each model is eventually shaped by a specific class of questions about such systems.

Conversely, a significantly high proportion of Supply Chain and Operations Management (SC&OM) research promotes a view of the researcher as tasked with discovering cause-and-effect relationships within an objective reality from which they postulate to detach themselves [17]. A common narrative in SC&OM is that an operations model is a miniature representation of a supply chain [18],

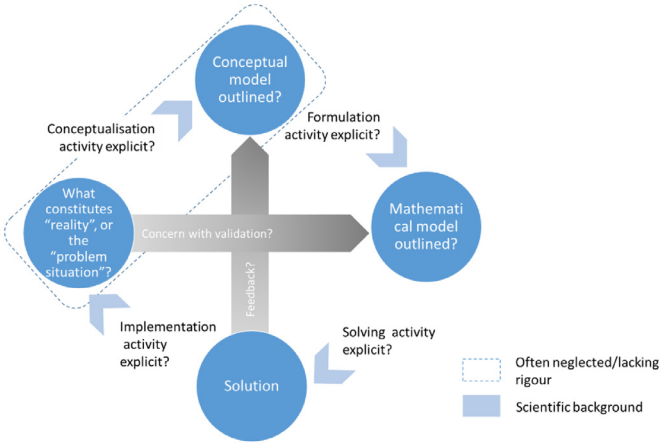

Fig. 1. Evaluation grid based on [15].

and the extent to which a model differs from the 'real thing', is a matter of comprehensiveness [19]. Insofar as sufficient quantitative data is available to populate a mathematical model, the problem situation is assumed to be well defined, and modelling a supply chain becomes a matter of implementing specific analytical tools [20–22]). This assumption is implicitly made in most models of healthcare systems [23], and pharmaceutical manufacturing [24].

Based on Wilson's [25] work on the analysis of organisation units a model is defined here as an intellectual construct explicitly describing a *way of thinking* about the real world. A model so defined acknowledges the perspective taken by an analyst who is making sense of a situation to reach a value judgment about it.

2.2. Theoretical lens

This paper adopts the systems view of OR, outlined by Sagasti and Mitroff [15], as the theoretical lens, hereafter referred to as the Sagasti–Mitroff research model. Although without explicit reference to supply chain modelling, the Sagasti–Mitroff research model captures generic aspects of the modelling activity, and it has previously informed methodological discussions in the SC&OM domain [19].

The fundamental dimensions to evaluate numerical and non-numerical aspects of PSC models proposed in the extant literature were derived from the Sagasti–Mitroff research model as shown in Fig. 1.

Unlike the original Sagasti–Mitroff research model, Fig. 1 does not identify a conceptual model with the analyst's own mental image of the problem situation. Rather, a conceptual model is understood here to be a description involving some degree of formalisation, for example in the form of supply network maps [26]; rich pictures [25]; and process diagrams [27].

2.3. Synthesis approach

Typically, the literature provides non-numeric evidence as it consists of words and symbolic data (e.g., text and equations). In the field of SC&OM the approach to content analysis, outlined by Seuring and Gold [28], is amongst the most explicit in terms of data gathering and data analysis, and has been used in works that explicitly take a supply chain modelling outlook (for example, [29,30]). Other works with a similar outlook tend to be less specific regarding the adopted approach for example [31,32]).

Methods for evidence-based research synthesis originally developed in healthcare research include, for example, Critical Interpre-

tative Synthesis (CIS), and aim to generate knowledge that goes beyond the conventional literature reviews by placing heterogeneous evidence in a coherent framework so that tensions and contradictions are exposed [33]. Tranfield et al. [14] discuss in-depth the advantages and limitations of extending the methods for evidence-based research synthesis developed in medical research to the management domain. In this research, CIS is used to generate synthesising arguments, through an interpretative process, which integrates quantitative and qualitative evidence from a heterogeneous body of knowledge, while explicitly questioning assumptions about the concepts and methods by which different solutions are derived.

Both primary and secondary research is the object of scrutiny in this paper. To enable content search the definition of 'modelling' provided in Section 2.1 was operationalised by including more specialised terms such as 'mathematical programming' and 'simulation', as well as more generic terms such as 'design' and 'analysis'. The following query was formulated to content search Web of Science for secondary research with an explicit supply chain modelling outlook, without restricting it to specific PSC applications:

(("supply chain" OR "supply network") AND review AND (Optim* OR simulation OR model* OR programming OR design OR analysis))

The search was limited to contributions written in English, published in peer-reviewed journals from 1998 (to coincide with the seminal review by Beamon [34]) in the following research areas: engineering, business economics, operations research, management science, computer science, and environmental sciences. The search initially generated 1744 results in Web of Science, of which 231 passed a first screening considering title, abstract and keywords to ensure that the point of focus was the use of models in SC&OM. Of these references, nine were specifically concerned with pharmaceutical and healthcare related issues, with two [9,35] used as a source of references for primary research. The publications retained are summarised in Table 1.

Primary research was identified over the last 5 years through a similar search query:

(("supply chain" OR "supply network") AND pharm* AND (Optim* OR simulation OR model* OR programming OR design OR analysis))

The refined search yielded 232 research papers, 38 of which were retained and expanded with 27 papers obtained from the selected reviews. Two references not included in the structured search were also added, one of which was a technical report. A total of 76 references were systematically collected through the reference management and knowledge organisation software Citavi 4 (www.citavi.com). Categories were initially derived from the secondary literature, and then modified and refined through the CIS approach as the analysis progressed to better reflect the emerging themes. From a procedural perspective, Citavi was used to assign categories to references as a whole, as well as to individual textual excerpts to allow retention of the meaning for text once it was removed from the context of specific studies, and in order to perform a meta-data-analysis [36]. A detailed classification of each research paper examined here is provided in Appendix A, Tables A.2–A.3.

3. Research findings

In this section, extant PSC models are evaluated in terms of their ability to enhance the analyst's understanding of the inherent characteristics of the specific system of interest [16]. For each research question outlined in Section 1, evidence is gathered from the literature on PSC models, consistent with a systems view of the OR activity (Section 2.2). A series of synthesising arguments are then formulated in Sections 3.1–3.4.

3.1. Synthesis of PSC definitions

Previous studies conceptualise the PSC as a 'complex adaptive system', and use such a concept as the object of empirical research [37]. This view echoes a more general tendency to acknowledge supply chains operate 'as a system', and hence should be conceptualised, modelled, and managed as such [12]. In particular, the supply chain is a system which encompasses elements and relationships that are socio-technical in nature [38].

The concept of *Healthcare Delivery System* (HDS) captures the broader ecosystem in which a PSC operates. According to the World Health Organization (WHO) an HDS consists of the organisations, institutions, resources, and people engaged in the equitable and efficient delivery of services that are critical to achieve an improved health status, whereby 'health' is not merely the absence of disease or infirmity [1]. Along with other medical supplies, the PSC contributes to the ability of an HDS to ultimately deliver healthcare service outcomes so long as medicines are available, affordable and safe [9].

To summarise, in principle *the PSC is a socio-technical system aimed to align firms in enabling the achievement of improved health status through medicines provision. Complementary and alternative products and process technologies may coexist within such a system.*

In practice, the most common approach in defining the PSC for modelling purposes is to 'follow the pill': in 80% of the reviewed references (henceforth, percentages refer to these references unless otherwise specified) the concept of supply chain is either implicit or it designates a more or less detailed breakdown of sequential activities (also echelons or stages) centred on the individual drug product as it progresses from its development stage to its final delivery (for example, [35]). A typical breakdown spans from drug manufacture until it reaches the point of dispensing to patient (57%); it rarely extends upstream to include raw materials (8%); often, boundaries are narrowed to include only the manufacture of Active Pharmaceutical Ingredients (API) and dosage forms (19%). Works that investigate the contribution of a PSC toward the achievement of some level of service to the patient through healthcare operations are also product-centric, since the provision of a 'service' is typically a synonym for a stock availability [39].

None of the examined definitions seem to provide a 'whole system', end-to-end perspective on pharmaceutical supply networks, which is necessary to evaluate emerging reconfiguration opportunities arising from a changing healthcare ecosystem [7,8]. Broadly speaking, a system must involve a combination of interacting discrete elements, which may be of a technical or social nature, organised in a structure fit to achieve some purpose [40]. These system-qualifying aspects can be found in most definitions of supply chain (see, for example, [41]). However, only 23% of the examined definitions explicitly state some specific purpose for the PSC ('alleviate suffering'; 'carry out a clinical trial' or 'ensure sufficient drugs for a clinical study'), and even less (13%) make a claim about its nature as a whole (namely a 'system'; an 'integration process'). This leads to the following synthesising argument:

> **Synthesising argument 1:** The PSC is mostly identified as a product-centric, linear sequence of stages which spans across the manufacture and physical distribution of medicines.

With regards to the context in which a definition of PSC is provided, research papers focus alternatively on new products being developed and tested, clinically trialled or commercialised, and this specification undoubtedly has practical relevance [42]. However, the conceptual definitions reviewed were deemed similar with regards to building blocks, links, scope and boundaries regardless of which type of context engages the underlying PSC. A similar reasoning applies to the case of emergency humanitarian supply chains [43].

Table 1
Literature reviews on pharmaceutical supply chain (PSC) with a modelling outlook.

Reference	Review Scope				Models reviewed			Key concepts				
	New Product Develop	Clinical trial supply chain	Drug product Manuf.	Distribution/Retail	Conceptual	Scientific	Solvers	Clinical trial supply chain	Pharmaceutical supply chain	Pharmaceutical enterprise	Healthcare supply chain	Emergency supply chain
Exclusively PSC												
[35]	•	•	•	•		•	•	•		•		
[9]	•	•	•	•		•			•		•	
[90]	•	•	•	•		•	•		•			
[97]				•	•				•			
PSC in a broader context (healthcare/process industry)												
[98]				•		•	•				•	
[43]				•		•						•
[52]			•	•			•		•			
[99]			•			•	•			•		
[100]	•	•	•			•	•	•		•		
[101]			•	•		•	•			•		

3.2. Synthesis of PSC conceptual models

Conceptual models of the PSC describe which phenomenon is of interest for the analyst, typically by use of a graphical representation. With specific reference to PSC, Srai et al. [7] apply supply chain mapping techniques to support an end-to-end, whole-system-level evaluation of PSC reconfiguration opportunities enabled by specific technology interventions. Seldom is the conceptual modelling of a system acknowledged as a rigorous modelling activity, and hence the difficulty in distinguishing the system of interest from its surroundings tends to be underestimated [44].

To summarise, in principle *the identification and representation of the system of interest within a PSC is an explicit and formalised activity aimed to delimit the areas of concern for the analyst by defining the scope and boundaries for the problem situation*.

Conceptual models were evaluated for 63 of the 67 research papers originally selected (4 were deemed out of scope after closer examination). The phenomena most represented by means of a PSC conceptual model include: distribution topologies (28% of cases); multi-facility production systems (23%); and workflows within individual facilities (25%). Fewer conceptual models represent organisational behaviours within the industry (11%); and Information Technology infrastructures (5%).

A PSC was modelled conceptually by means of diagrammatic 'nodes-and-arcs' structures in 83% of cases. However, only 22% follow a formalised technique to outline such diagrams. Examples include techniques developed in the domain of Process Systems Engineering, such as State-Task-Networks (STN) and process diagrams, or System Dynamic's causal loop diagrams. However, causal loop diagrams represent connections between variables identified within the formulation of a mathematical problem rather than between the elements of a PSC. Conceptual models of digital infrastructures are the subject of a specialised type of diagrammatic representation, employed to explore the implementation of specific solutions, for example, inventory management across the PSC [45,46], and the tracking of counterfeit drug products[47]. In all the other cases, the meaning attributed to the nodes and arcs in a diagrammatic representation is left to the researchers' discretion, and hence varies significantly across studies.

Other approaches are used to represent the broader ecosystem of a PSC. Compton et al. [23] use an unstructured pictorial representation to model the elements of a HDS: patient, care team, organisation, and political and economic environment. Although without declaring it explicitly, Yang et al. [48] use a 'rich picture' to illustrate the application of printed electronics in intelligent medicine packaging to collect health data through a homecare platform.

Finally, an often-overlooked aspect of conceptual modelling is whether, and to which extent, the outlined model is underpinned by a rigorous collection and analysis of qualitative data. In 77% of the selected items this aspect is omitted. Only 11% of cases mention the analysis of qualitative data elicited from survey respondents or interviewees as part of the research methodology. However, when the emphasis is placed on mathematical modelling the use of qualitative data analysis, if any, is largely undisclosed. Exceptions include works such as [49] and [50], which are based on System Dynamics; and [51], where a fully-specified case study research underpins the formulation of a mathematical model of the PSC.

This leads to the following synthesising argument:

Synthesising argument 2: Most conceptual models of the PSC consist of loosely formalised diagrammatic representations of heterogeneous objects of analysis, such as whole organisations; distribution topologies; digital infrastructures; multi-facility production systems, or workflows within individual facilities. Occasionally, such diagrammatic representations are underpinned by qualitative data analysis.

3.3. Synthesis of PSC mathematical models

End-to-end analysis of the PSC 'as a system' is crucial to inform an integrated system re-configuration agenda. This enables the identification and assessment of the key metrics that quantify the potential repercussions of targeted transformation scenarios [7,8]. Mathematical models are formalised through a language deemed less ambiguous and can be manipulated to generate solutions [15,16]. In particular, *a mathematical model of the PSC should enable the analytical evaluation of its current and alternative states in terms of structural and behavioural characteristics, in response to changes in market demands, patient needs, and resources availability*.

Existing classifications focus more on model-solving techniques than on PSC models per se (for example, [52]). Mathematical models of the PSC were identified by examination of the equations reported in the reviewed items, if any. In the majority of cases a model of the PSC was embedded in mathematical programming-type models meant to optimise some figure of merit, such as in production-delivery system planning [32], strategic game-theoretic models [53], and statistical Data Envelopment Analysis [54]. These broader models share a similar constrained optimisation intent, despite being typically assigned to distinct categories (for example, [29]).

Detailed PSC models from 50 items were synthesised, after excluding some items due to lack of relevant mathematical contents, or because saturation was reached. These models were grouped according to "archetypes", derived by CIS, rather than enumerated according to the modelling approach claimed. Each archetype is discussed separately in the following Sections 3.3.1–3.3.3.

3.3.1. Archetype I: supply and demand matching mechanism

Approximately 54% of mathematical PSC models presented in the reviewed references represent a supply and demand matching mechanism within a multi-echelon production-inventory system, henceforth referred to as Archetype I.

The key features exhibited by mathematical PSC models synthesised here as Archetype I can be summarised as follows, using [55] as a case exemplar for illustrative purposed:

- One or more discrete "slices" are taken along the time axis. In the example, time slices are 1-month long time periods over a 1-year long time horizon.
- Within a time slice, a set of elements and links between such elements are identified according to specified scope and boundaries. In the exemplar case, the boundaries correspond to a single manufacturing site, within which three distinct business units operate, each one specialised in a dosage form manufacturing and packing. The scope includes each activity/task performed by each piece of equipment; the material conversions taking place in each business unit to bring about a range of products; the purchase of raw materials or extra capacity if needed, and the sale of finished products.
- The links between elements included within the boundaries and described to a level of granularity consistent with the scope are logical relationships of technological or chronological precedence. In the exemplar case, the activities are linked through material 'input–output' relationship defined by the relative amounts of materials required or resulting from a reference unit of activity level (one ton of product)—also called 'technological coefficients'. The utilisation of operant resources such as equipment by activities is also expressed through a coefficient called activity-facility ratio.

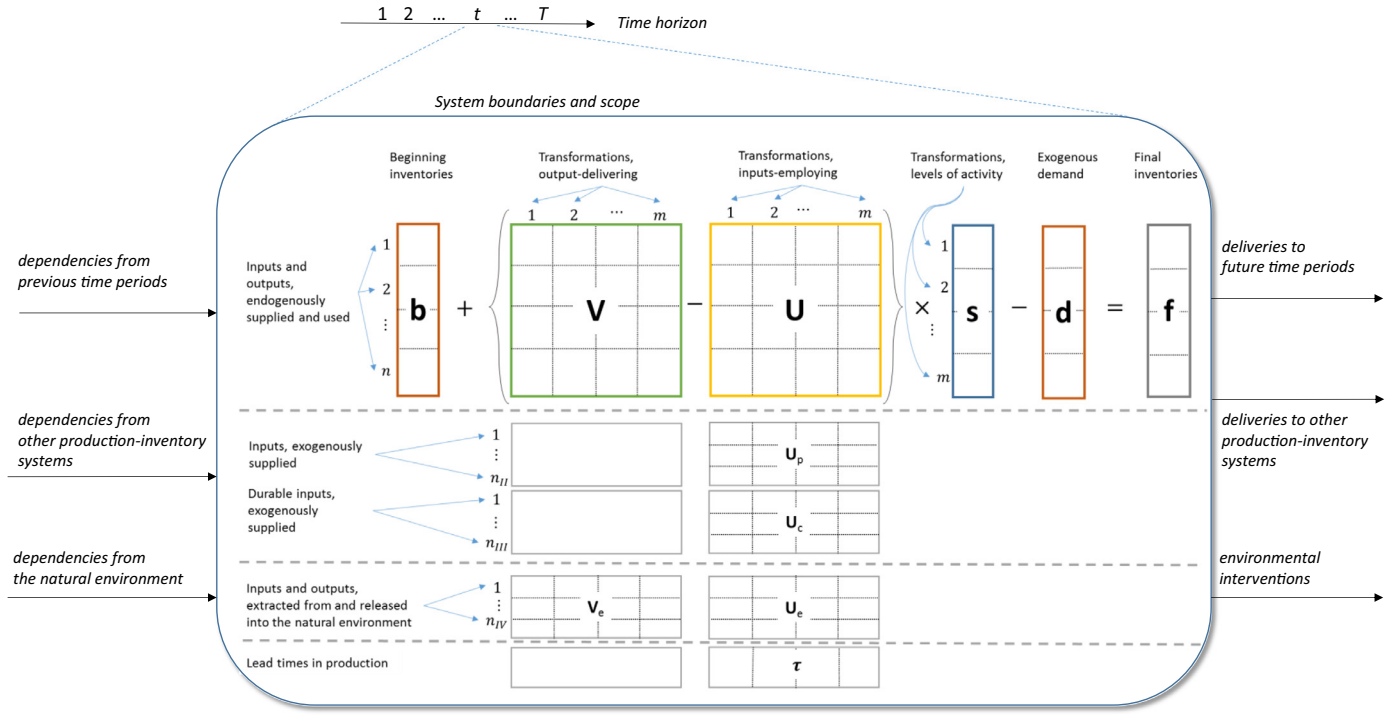

Fig. 2. Synthesised model of the PSC as an inter-temporal demand–supply matching mechanism within a production-inventory system. Table 3 provides details on the notation used.

- While some aspects of the modelled PSC are known, other aspects need to be determined by means of computation. In the exemplar case, the technical coefficients are known and remain unchanged over time, but the level at which each activity must operate, and the final inventories in each time period are unknown variables. The resulting network configuration is therefore fixed, as the main unknown is the strength of the links between the PSC elements, not whether such links exist.
- In general, input–transformation–output structures are underpinned by *technological knowledge* [56], which may or may not be addressed explicitly in a mathematical model. The example does not specify the modelled products, materials and manufacturing technologies (such as batch or continuous), although some of the manufacturing steps are mentioned explicitly, and so are the dosage forms.

The above mentioned features can be formalised concisely through a set of vectors, matrices and basic algebraic operations connecting them. The suggested formalised representation of Archetype I models is illustrated Fig. 2 and Table 2 and discussed below.

Quantified dimensions of the PSC: The dimensions of a PSC represented in a mathematical model (such as time periods, locations, equipment, activities, materials) are often organised hierarchically, and captured in the equations through a number of indexes that vary from study to study. With reference to the reviewed models the following was found:

- The columns in matrices U and V (rows in vector s) reflect a combination of sites/locations (85% of the reviewed models), time periods (75%), tasks/activities (35%), geographies (32%), scenarios (25%), and campaigns (14%).
- The rows in matrices U, U_p and V (and in vectors b, d, and f) reflect a combination of product categories such as raw materials, final products and intermediates (97% of the reviewed models). Further distinctions include, for example product families and compound stability classes (14%).
- The rows in matrix U_c typically reflect types of manufacturing equipment or storage facilities, and the capacity which is being utilised (35% of the reviewed cases).
- The rows in matrices V_e and U_e are often of little or no relevance. The possibility of a drug product turning into waste, for example, if unused at the end of a clinical trial or if a change in policy and legislation occur is considered in 21% of the reviewed models. However, a detailed identification of environmental resources utilised (for example water), and pollutants released into the natural environment (for example carbon dioxide) is limited to models that are specifically developed in the domain of environmental Life Cycle Assessment, such as [57].
- Lead times in production, forming the entries of vector τ, are specified in almost 60% of cases. Lead times mostly refer to clean ups and set ups, especially in models where data is specified by "campaign", which is a characteristic of batch manufacturing.

Known parameters and variables to be computed: The main parameters that must be known in Archetype I PSC models are the preconditions and post conditions that must be observed in production, or technical dependencies. These are often expressed in terms of input linkages captured by the elements in matrices U, U_p, U_c, and U_e; and output linkages captured by the elements in matrices V and V_e. In 39% of the reviewed models the magnitude of these technical dependencies is given as a "cookbook recipe", an example of which are the technological coefficients in [55]. In 36% of cases, matrices U and V only contain ones and zeros, implying that the amount of product delivered at one echelon of the PSC is entirely transferred to another (for example, [51]). In most Archetype I models, an exogenous demand f summarising patient consumption, is also known or knowable. Conversely, the main variables to be determined are the elements of vector s, which represent whether the corresponding transformation step is performed and, if so, at which level it should operate. In 4% of

Table 2
Explanation of matrices and vectors used to represent purposeful transformations in Archetype I.

Notation	Description	Represented aspect	Rows	Columns	Generic element	
Temporal and downstream decoupling						
$\boldsymbol{b}$	Vector of beginning inventories at time t	Dependencies from previous time periods	Endogenously supplied and used inputs/outputs (e.g., intermediate and final products), indexed as $i = 1, \ldots, n \in \mathbb{N}$	N/A	$b_i \geq 0$	Amount of 'operand' resource i available at the beginning of the time period considered, expressed in appropriate units
$\boldsymbol{d}$	Exogenous demand vector	Deliveries to other economic systems	As above	N/A	$d_i \geq 0$	Non-controllable demand forecast to be met through the system's final deliveries.
$\boldsymbol{f}$	Final inventory vector	Deliveries to other time periods	As above	N/A	$f_i \geq 0$	Amount of i available at the end of the time period considered
Level of activity						
$\boldsymbol{s}$	Activity level vector	System behaviour	Transformations defined according to the technological knowledge available and the a level of granularity, indexed as $j = 1, \ldots, n \in \mathbb{N}$	N/A	$s_j \geq 0$	Level of activity of each transformation stage e.g., product volume; selection/not selection of a specific transformation etc.
Technological dependencies						
$\boldsymbol{U}$	Technological pre-conditions (inputs)	Within-boundaries structural dependencies between purposeful transformations	As above	Purposeful transformations characterised according to the technological knowledge available and the desired level of granularity, indexed as $j = 1, \ldots, n \in \mathbb{N}$	$u_{ij} \geq 0$	Amount of 'operand' resource i to be acted upon for producing an effect by executing j, expressed for a reference level of activity of j (for example, one unit of output, one operating hour, one time period)
$\boldsymbol{V}$	Technological post-conditions (outputs)	As above	As above	As above	$v_{ij} \geq 0$	Amount of i delivered by an accomplished execution of j at a reference level of activity
$\boldsymbol{U_p}$	Transactions with exogenous suppliers	structural dependencies with transformations outside the system's boundaries	Inputs not provided by any transformation within the system boundaries (e.g., raw materials, energy), indexed as $i = n+1, \ldots, n_{II} \in \mathbb{N}$	Purposeful transformations characterised according to the technological knowledge available and the desired level of granularity, indexed as $j = 1, \ldots, n \in \mathbb{N}$	$u^p_{ij} \geq 0$	Amount of 'operand' resource i to be acted upon for producing an effect by executing j, expressed for a reference level of activity of j
$\boldsymbol{U_c}$	Asset utilisation	As above	Durable inputs not provided by any transformation within the system boundaries (e.g., equipment, personnel) indexed as $i = n_{II}+1, \ldots, n_{III} \in \mathbb{N}$	As above	$u^c_{ij} \geq 0$	'operant' resources, employed to act upon the 'operand' resources throughout multiple executions of j, expressed for a reference level of activity of j

cases, both the presence or absence of technical dependencies, and the magnitude of such dependencies, are variables to be simultaneously determined by solving the model (for example, [58]). Inventory levels at the beginning and end of each time period, represented by vectors b and d, are also unknown variables that must be computed. In 25% of cases the focus is shifted away from manufacturing, and towards multi-echelon inventory systems where most activities relate to replenishing inventories of pharmaceutical products (for example, [59]). However, some inventory models focus exclusively on known demand and cost parameters, rather than on the technical and temporal dependencies between the activities taking place in a PSC, when computing variables such as the 'optimal' order quantity and reorder points [39,42]. Technical dependencies in production are mostly omitted also in models that focus on behavioural aspects of organisations (for example, [53,60]), or investment decisions (for example, [61]). In all these cases the input structure (matrix U) is typically irrelevant, whereas the dimensions of matrix V and vectors, b, d, s and f reduce to one finished product, multiple time periods, and possibly multiple locations.

Inclusion of time in the computations: With regards to temporal dynamics, in 60% of Archetype I models two consecutive time slices are connected by 'moving' inventories from one period to the next. In 25% of the models, time plays no role since the focus is on a 'static snapshot' of a PSC over a pre-defined time horizon with no analytical linkages to past or future periods. Conversely, 15% of the models are time-lagged, meaning that the presence of non-zero lead times (vector $\boldsymbol{\tau}$) in production creates linkages across non-adjacent time slices (for example, [51]). In some cases time lags are due to the expansion of production capacity, as in new plant construction [61] or to the specification of shelf life for individual materials and products [62]. Non-manufacturing models of the PSC are mostly concerned with determining optimal replenishment and safety stocks ahead of a planning horizon, and therefore do not necessarily depict how production and inventories unfold dynamically over time (for example, [42]).

Disclosure of technological knowledge about products, manufacturing and digital technologies: Almost all the Archetype I models reviewed are not affected by the underpinning product and manufacturing technology. In 52% of the reviewed papers manufacturing technology is generically described as batch (37%), continuous (7.41%), or both but has no immediate repercussion on the mathematical model formulation (for example, [58,61]). Only one Archetype I model makes the case for the introduction of a digital Information Technology to improve inventory management in home healthcare provision [63].

In summary, this leads to the following synthesising argument:

> **Synthesising argument 3(a)**: Most models represent the behaviour of a PSC as a mechanism to align supply and demand of medicines and related materials across a multi-echelon production-inventory system, where the structure of such a system is defined in terms of technical and temporal dependencies. Typically, the patient's condition is outside the boundaries of a PSC, and the technology interventions in manufacturing and information management remain implicit.

3.3.2. Archetype II: generalisation models

Archetype II models make up 8% of the reviewed cases. This archetype includes models in which some operational aspects of a PSC are evaluated by means of generalisations obtained through statistical associations or subjective judgment. They typically are aimed at overcoming a detailed, mechanistic modelling of a PSC from first principles, which is a characteristic of Archetype I. Being computationally heterogeneous, Archetype II models will be discussed case-by-case, rather than by attempting a synthesis of a common underpinning mathematical formulation as in the previous section.

Most Archetype II models are data-driven, meaning that they aim to "make sense" of an existing track record of empirical evidence by fitting some exact mathematical approximation to it. Typically, these data-driven models yield a 'summary statistic' which quantify a specific aspect of a PSC echelon based on available data. For example, Kumar et al. [64] describe a number of medicine distribution and dispensing business units in terms of historical data about expenditure and sales over multiple time periods. The efficiency of inputs utilisation at each unit and at different points in time is then computed by solving a mathematical programming model which is characteristic of Data Envelopment Analysis (DEA). Another application relies on data across a number of API manufacturing batches to generalise by statistical inference the relationship between informative manufacturing parameters and cumulative energy consumption [65]. Batch manufacturing data also provide the basis to estimate variability in lead times as a probability density function with unknown parameters [66].

A somehow different kind of Archetype II model is one in which the empirical data gathered consists of subjective judgments, for example in the form of scores given by experts on the relative importance of certain aspects of the PSC. Example range from hypothesised severities of hazards occurring due to tainted or counterfeit drugs [67], to the application of Analytical Hierarchy Process to develop priority weights in manufacturing and packing for specific Stock Keeping Units [68].

In summary, this leads to the following synthesising argument:

> **Synthesising argument 3(b)**: Generalisation models are meant to identify and estimate explanatory or hierarchical relationships between quantifiable attributes of a PSC from either past evidence or subjective judgment. While the techniques used to this purpose vary, their common aim is to overcome the need for a detailed, mechanistic understanding of the PSC as a system for modelling purposes.

3.3.3. Archetype III: outcome-based models

A group of models referred to here as 'Archetype III' (18% of the reviewed models) share an interpretation of the PSC as a collection of possible 'states' of the world as well as the consequences associated to transitioning form one state to another.

Central to most Archetype III models is the enumeration of scenarios that could unfold as some uncertain variable reveals itself over time, for example the outcome of a consecutive clinical trials for new pharmaceutical products. The enumerated outcomes are typically assessed based the possible sequences of occurrence, and some quantification of resources needed in the case of a specific realisation (see, for example, [69]).

In the vast majority of cases, Archetype III models are models of a 'pipeline' in the development of new drug products, where a variety of molecules compete for similar resources but differ in terms of chances of commercialisation, and hence need to be accorded priority. However, this is not the only context in which Archetype III arises. For example, some models with an emphasis on drug preparation and administration scheduling were classified as Archetype III, rather than Archetype I, due to their emphasis on transitioning between possible states (for example, patients visited [70]) over what is supplied, how it is supplied, and to meet which demand. Some models which embed elements of both Archetype I and III were classified under the former for the opposite reason (such as [71]). Example of how an Archetype III model enters the formulation of an Archetype I model include [72] and [71].

Similar to Archetype I models, the basic diagrammatic representation in Archetype III models consists of nodes and directed

arcs connecting those nodes. Typically, nodes are interpreted as possible scenarios or states, and arcs as chronological rather than technical precedence i.e., arcs do not represent some physical or information flow across nodes, rather, they represent the possibility of 'moving' from one node to the other as well as attributes associated with such transition (e.g., probability of occurrence, distance to be travelled etc.). Another similarity with Archetype I models is that the presence or absence of a precedence relationship between two nodes may be either given or determined as part of the models solution procedure as in, for example, [73].

In summary, this leads to the following synthesising argument:

Synthesising argument 3(c): outcome-based models are often used to represent stochastic relationships between states of the world that occur stochastically as part of the research & development pipelines and launch scenarios for new pharmaceutical products, rather than relationships between the elements that constitute the structure of a PSC.

3.3.4. 'Black-box' algorithms and semi-quantitative models

A residual category consists of those models where mathematical notation is either insufficiently disclosed to classify the model as one of the archetypes discussed in Sections 3.3.1–3.3.4, or the model is based on 'hybrid' approaches where elements of conceptual and mathematical modelling coexist. About 20% of the reviewed models fall into this residual category.

Some 'black-box' approaches may actually disclose the underpinning model of the supply chain via a*lgorithms* rather than in mathematical terms, that is, using a sequence of instructions framed according to certain syntax, as in a flow chart or a computer programming language. Examples include agent based models (for example, [74]) and other models where the emphasis is placed on the results of a simulation and optimisation (for example, [75]).

Hybrid models of the PSC, by contrast, typically are framed following the formalisms of *system dynamics*. These models typically consist of a representation of the causal loops between operational variables that supposedly express the behaviour of the PSC, and accompany such a representation with an indication of the 'direction' and nature of the relationships (for example [49,50]). While these models have, in principle, an underlying mathematical counterpart [16] this was not disclosed in the reviewed works.

3.4. Economic aspects in PSC models

The main economic aspects of the PSC, captured by the reviewed models, are cost, revenues and demands. The structure of payments being a distinguishing feature of the relationship between a PSC and the healthcare system of a specific country, this structure is typically captured in conceptual models such as [76,77], rather than in mathematical models of the PSC.

Cost is a prominent economic aspect in Archetypes I and III. Although with a varying level of granularity across all the reviewed models, cost is attributed to products by direct costing, where the direct product costs involved may be fixed or variable with respect to product volumes (see, for example, [78]). More sophisticated costing approaches such as Activity Base Costing and Cost of Quality are rarely applied in a PSC context, and are typically disconnected from the formulation of engineering PSC models (for example [79,80]).

Generally, unit values for 'cost' and 'revenues' are known model parameters that are meant to be multiplied with some level of activity once determined by solving a specific PSC model (for example the amount of material or batches produced in a facility; or the capacity level after investment in additional facilities). Although some works frame production costs as functions, these are typically fixed upfront as in, for example, [53]. Costs and revenues thus determined are then combined in a figure of merit—typically in the form of profit or net present value—to be optimised to eventually determine some 'optimal' configuration and level of operation of the PSC.

With regards to Archetype I models, the most occurring unit monetary worth parameters include: inventory holding (75%); manufacturing (57%); final drug product (54%); penalties and opportunity costs (39%); transportation and distribution (32%); product scrapping (25%); setups and clean-ups in batch manufacturing (22%); investment in new or expanded capacity (22%); purchase orders placement (18%); raw materials (14%); taxes and import duties (11%); quality control (11%). Only a few works consider other cost items such as packaging costs, R&D costs, marketing and sales costs, labour cost and equipment depreciation. Conversely, the main example of economic PSC aspects in Archetype II is the use of data points expressed in monetary units. For example, the main dataset used in [64] consists of monthly sales and advertising expenditures. For archetype III, it is common to refer to 'resources' employed in the new product pipeline (e.g., testing facilities), and to assign a given monetary worth which is assumedly known upfront. Assumptions that link revenue to the time a new product is introduced to market are also common, for example [69].

Demand is an aspect mainly related to Archetype I models. In the absence of end-to-end visibility through real-time collection and communication of biometric patient data, the demand of drug products is typically considered to be exogenous element and forecasted rather than managed. Seldom is a detailed demand forecast using patient-based or prescription-based approaches [81] incorporated in a PSC model. In 22% of cases, demand is stochastically generated—for example, the demand over lead in the case of clinical trial inventory modelling [42]—and in 75% of cases it is a given, as in production scheduling problems [58], or expressed in some functional form specified upfront—such as linking demand with market price elasticity [82]. Among the few exceptions, Hansen and Grunow [51] use insights from case study research to formulate stochastic demand generation for a new drug product.

In summary, while economic aspects are crucial to model the configuration and behaviour of a PSC the determination of such aspects is not at the heart of the PSC modelling intent. In most cases, economic aspects are parameters assumed to be known or easily knowable, and economic evaluations across the PSC almost exclusively consist of a direct costing exercise.

3.5. Solution approaches and implementation

The evaluation grid in Fig. 1 includes activities in solving mathematical models formulated, and also takes into account the actions in implementing the solution thus determined in real world settings. As outlined in Section 2, most existing reviews place the focus on how mathematical models of the supply chain, in general, and the PSC in particular are solved.

Circa 14% of the reviewed references did not specify how the mathematical model presented was solved. Explicitly mentioned solution methods include algebra (5%), optimisation algorithms (42%) although in most cases the insights provided is limited to a reference to the off-the-shelf solver employed (exceptions include, for example, [59]); numerical methods such as simulation (5%); and undisclosed algorithmic approaches (28%) including artificial intelligence methods; and heuristics (7%).

For most reviewed papers do not report on whether the models outlined were implemented in real-world settings, and what were the implications. Among the few exceptions, [55] explicitly provides an application to solid dosage manufacturing in India, none of the reviewed references specifies whether any action

was taken by businesses based on the solution obtained for the proposed PSC model.

4. Discussion

In this paper, a selection of extant models was evaluated in terms of their ability to enhance the analyst's understanding of the inherent characteristics of a PSC as the system of interest. A systems view of OR enabled the identification of some archetypal aspects of PSC modelling throughout the typical activities undertaken by the analyst, from the identification and conceptualisation of the relevant system, through the formulation and solution of mathematical models, to the implementation of the obtained solution to inform managerial practices. These findings, as well as the possible implications for theory and practice in the light of the challenges currently faced by the pharmaceutical industry are summarised in Table 3, and discussed below.

4.1. System identification

As outlined in the introduction, traditional pharmaceutical manufacturing is now facing challenges associated with the need for more patient-centric supply chains capable of delivering greater drug product personalisation; in supporting more participative healthcare through digital medical devices; and leveraging advances in novel continuous processing to enable more dispersed and responsive manufacturing models. Higher-level narratives tend to emphasise the intrinsic merits of single interventions aimed at attaining improved healthcare outcomes through, for example, innovative manufacturing technologies. Rigorous analytical frameworks to capture PSC reconfiguration opportunities from a 'truly' end-to-end/whole-system perspective have been proposed [7], but operate mostly at the conceptual level.

Seldom does a definition of PSC adequately highlight other distinctive features of the underpinning phenomenon than the final product delivered. Most definitions fail to address the 'system' qualification of a PSC, and to frame its aims with the patient and the treated condition in mind. In some cases, it is difficult to distinguish between the purpose of a PSC and the constraints imposed on how such a purpose should be achieved, for example "cost effectively", or "with minimum environmental impact". Insights into a possible definition of PSC are offered in Section 3 (research findings). An explicit reference to the notion of system is sufficient to address the presence of multiple, purposeful elements in a PSC and the linkages between them. The social and technical nature of such elements characterises the general concept of supply chain [38], but the intended final delivery should be distinctive of a PSC.

The term 'network' is often used along with 'system' to enrich the concept of PSC, and sometimes it pinpoints the fact that a firm may be simultaneously part of multiple supply chains [83]. More often its meaning is simply left to interpretation. In line with previous research [12,38], the concept of network should be used to describe specific architectural structures that may be observed in a system, and to direct the attention towards a specific analytic lens to evaluate such structures.

To enable further research, for example through testable propositions, a specific definition of PSC should be evaluated according to the rules of formal conceptual definition outlined by Wacker [84]. For illustrative purposes, such rules are applied to compare the PSC characterisation suggested in Section 3.1 with a selection of generic definitions of supply chain, as shown in Appendix B.

The above leads to the following implications:

- From a theoretical perspective, the point of focus of PSC models should shift from the volumes of individual pharmaceutical products moved across the supply network, to the healthcare outcomes these volumes contribute to attain (or not). This could be achieved by introducing the concept of "functional unit", which is well-established in modelling end-to-end environmental aspects, to formalise a pharmaceutical product "in use".
- From a practical perspective, it is key to realise that, while current models of the PSC may help with "polish the factory", the benefits of local optimisation could be offset by the dynamics of complex distribution and healthcare delivery systems, as well as patient behaviour in the downstream segment of the PSC. Currently, these aspects are treated as a 'black box' in PSC modelling, and addressed aggregately through demand forecasts.

4.2. System representation

In principle, it is desirable to simultaneously develop a pictorial representation and a mathematical model of the system under study to ensure that the interrelationships within such a system are appropriately captured [16]. Despite the seminal work of Sagasti and Mitroff [15] conceptual and mathematical modelling continues to be the province of specialist approaches—e.g., supply chain mapping though case study research, and supply chain design and optimisation—and hence tend to be developed in isolation, and are not meant to complement each other. For example, works such as Watson et al. [22] recognise the value of using supply chain maps to achieve a common understanding of the problem situation within inter-disciplinary teams involved in a network design project. However, the topic appears to be subordinate to, and is approached with less methodological rigour than the mathematical aspects of modelling. With specific reference to PSC, seldom is a structured approach to supply chain mapping employed. Rather, diagrammatic representations, if any, are unstructured and decoupled from the computational aspects of a PSC model (for example, [85,86]). In other cases, a pictorial representation is used for the sole purpose of illustrating the variables in a mathematical model of a PSC (for example, [42,69]). Exceptions such as [51] explicitly link the formulation of a mathematical model of the PSC for use in planning new products market launch, building on evidence from qualitative data gathered through case study research. Although only conceptually, Srai et al. [7] outline an approach to network design and systems integration where industrial systems analysis and supply chain mapping techniques coexist with, and complement, an analytical evaluation of current and future states of a pharmaceutical supply network.

The above leads to the following implications:

- From a theoretical perspective, mapping the current state of a PSC, as well as the re-configuration opportunities arising from specific technology interventions should be regarded as a necessary premise to the formulation of meaningful and defensible mathematical models of the PSC. This requires a shift from regarding PSC mapping as a "nice to have" in addition to mathematical modelling, to considering it as an integral part of the systems view of OR, to be approached with methodological rigour and supported by evidence.
- From a practical perspective, mapping current and future PSC configurations is necessary to establish realistic boundaries conditions (breadth) and scope (depth) when exploring the relative attractiveness of potentially disrupting technology interventions e.g., in medicine manufacturing or healthcare management from an OM&SC perspective, thus ensuring consistency and "like for like" comparisons when mathematical models are implemented.

Table 3
Summary of findings and gap identification.

Modelling phase (Research question)	Proposed conceptualisation	Synthesising argument based on literature	Gaps and recommendation
System identification: (What is meant by PSC?)	The PSC is a socio-technical system aimed to align firms in enabling the achievement of improved health status through medicines provision. Complementary and alternative products and process technologies may coexist within such a system	The PSC is mostly identified as a product-centric, linear sequence of stages which spans across the manufacture and physical distribution of medicines	Currently, a rigorous 'system' qualification of the PSC and a patient-centricity perspective is lacking. While current models of the PSC may help with "polish the factory", the benefits of local optimisation could be offset by the dynamics of complex distribution and healthcare delivery systems, as well as patient behaviour in the downstream segment of the PSC. Future models should therefore address which healthcare outcomes the PSC must contribute to attain for pharmaceutical products to deliver value "in use". Greater compliance with theory of formal conceptual definition should be sought to generate propositions concerning the PSC that can be appropriately tested and therefore facilitate further research.
System representation (Which phenomenon is represented in a model of the PSC?)	The identification and representation of the system of interest is an explicit and formalised activity aimed to delimit the areas of concern for the analyst by defining the scope and boundaries for the problem situation.	Most conceptual models of the PSC consist of loosely formalised diagrammatic representations of heterogeneous objects of analysis, such as whole organisations; distribution topologies; digital infrastructures; multi-facility production systems, or workflows within individual facilities. Occasionally, such diagrammatic representations are underpinned by qualitative data analysis.	With rare exceptions, qualitative and quantitative models are developed through 'silos' approaches. Most mathematical models of the PSC are decoupled from a rigorous conceptualisation and representation of the problem situation, namely the current and future state of the system of interest. A shift is required from regarding PSC mapping as a "nice to have" in addition to mathematical modelling, to considering it as an integral part of the systems view of OR, to be approached with methodological rigour and supported by evidence The practical benefits of such shift is the ability to establish realistic boundaries conditions (breadth) and scope (depth) when exploring the relative attractiveness of potentially disrupting technology interventions in terms of PSC reconfiguration.
System quantification (How is the modelled PSC quantified?)	A mathematical model of the PSC enables the analytical evaluation of the current and future states of multi-tier supply networks trough quantifiable metrics that adequately reflect its structural and behavioural characteristics in responding to changes in market demands and patient needs while ensuring an end-to-end efficient use of resources	Archetype I models represent the behaviour of a PSC as a mechanism to align supply and demand of medicines and related materials across a multi-echelon production-inventory system, where the structure of such a system is defined in terms of technical and temporal dependencies. Typically, the patient's condition is outside the boundaries of a PSC, and the technology interventions in manufacturing and information management remain implicit.	Within Archetype I, models of the PSC tend to specialise in representing silos of activity such as manufacturing, inventory management, and distribution: An end-to-end, customers-centric perspective is therefore absent thus making it difficult to make a reliable business case to evaluate opportunities arising from technology interventions. To enable future research an archetype I PSC model should clearly address the following elements: • Functional unit, ideally capturing one or more pharmaceutical products "in use"; • Boundaries and scope, specifying which variables are exogenous (for example, demand), which elements of the delivery system are included; and what are the relationships between such elements in terms of technological and temporal dependency • Underpinning technological knowledge; • Assumptions about sources and nature of underpinning data (for example, real-time data streams versus "one off" data snapshots)
		Archetype II models are meant to identify and estimate explanatory or hierarchical relationships between quantifiable attributes of a PSC from either past evidence or subjective judgment. While the techniques used to this purpose vary, their common aim is to overcome the need for a detailed, mechanistic understanding of the PSC as a system for modelling purposes.	Archetype II models are data-driven in the sense that presuppose the existence of empirical evidence in the form of a data pool. Insofar as adequate data is available, these models can be useful to explore explanatory relationships between specific, quantifiable attributes of a PSC. To enable future research Archetype II models should prioritise replicability by greater transparency of the following: Data sets (retrospective observations; elicited subjective opinion) and modes of collection Inference and ranking mechanisms • Exploration of the underpinning data given the nature of the represented variable (for example categorical as in scores, or continuous) • Suitability of the underpinning method of analysis (for example parametric, or non-parametric) to the nature of the modelled phenomena • Reliability, validity and 'goodness of fit' considerations
		Archetype III models are often used to represent stochastic relationships between 'states of the world' that occur stochastically as part of the research & development pipelines and launch scenarios for new pharmaceutical products, rather than relationships between the elements that constitute the structure of a PSC	Little or no detail is provided on how the probabilities of transitioning between states of the world in Archetype III models come about (for example, as a result of analysing a historical track record of empirical evidence or by eliciting knowledge from experts). A clearer link with the empirical evidence underpinning these models is therefore required. Linked to this aspect is the need to address the theoretical nature of quantifying probabilities, leading to whether a Bayesian or a frequentist approach is more suitable. Also, it may be worth exploring similarities and differences between Archetype III models used upstream in the PSC, for example to model product portfolio pipeline, and those used downstream to model the arising complications for patients conditions such as diabetes

4.3. System quantification

In the quest for the "best" supply chain configuration design, seldom are the merits of engaging in some kind of optimisation exercise questioned. PSC models are simply expected to become increasingly sophisticated, and to deliver exact numerical solutions to problems involving competing social, environmental and economic objectives, and a prohibitively large number of variables [31]. A common oversight is that a mathematical model of an industrial system is useful insofar as it aids in understanding that system—with no implication that the results need to be perfect [16]. By developing strong anchoring points in the way a problem is framed and structured through a model operation researchers may put at risk their ability to observe, understand and manage the system created by the modelling process [87].

Although with a focus on survey research in SC&OM, Melnyk et al. [88] emphasise the importance of full disclosure of the techniques used in the extant literature, and explicitly identify a minimum amount of information that should be disclosed by the analyst to improve the accumulation of knowledge through the application of such techniques. In a similar fashion, the key elements to assess the quality of each PSC modelling archetype identified in Section 3 are summarised in Table 3, along with recommendations on how to overcome some of the current specific limitations.

From a real-world application perspective, as pharmaceutical products become more complex, individualised and on-demand, new production technologies such as continuous manufacturing, process analytical technologies, and nano-structured drug delivery systems processing are needed to augment the classical manufacturing routes [89]. However, the findings of this research suggests that an understanding the underpinning manufacturing and information technologies, aggregately referred here with the term technological knowledge, currently play a limited role in the formulation of PSC models. While this appears in line with the point that in the pharmaceutical industry, plant design tends to be very traditional, with no real change in manufacturing technology for 50 years [90], it seems legitimate to wonder how can the analytical tools developed in such a context can support an evaluation of emerging reconfiguration opportunities arising from medicine manufacturing and more patient-centric business models. Most models of the PSC are developed with production planning and scheduling in mind, rather than in comparing the merits of alternative product or process technologies or business models. Although with reference to environmental aspects only, PSC models have been developed with a Life Cycle Assessment approach that are inherently comparative in nature (for example, [91]).

Information flows and the use of digital technologies is also an emerging topic, which plays a limited role in the formulation of current PSC models. With the exception of Archetype II models, which are inherently data-driven, most PSC models do not provide insight into how the data, which supposedly are needed to populate them, are to be generated, stored, retrieved and transmitted. Models, by contrast, entirely devote themselves to Information technology solutions such as, drug anti-counterfeiting [47], Vendor Managed Inventories [46], and hospital inventory management [45] and confine themselves to the design of the digital infrastructure necessary to the purpose at hand. Less structured representations are also used to model conceptually patient-centric digital homecare solution [48,63].

Economic considerations are present in 90% of the reviewed references, typically in terms of product-related 'cost' and 'revenues'. However, the economic aspects become apparent only when the PSC is embedded in a 'broader' modelling exercise. In 90% of the cases, economic values such as 'cost' are assumed to be common knowledge data rather than metrics that need to be determined through a modelling effort. Although without specific reference to the PSC, concepts such as Total Cost of Ownership [92], and Supply Chain Costing [93] have long addressed the complexities related to estimating and managing costs beyond the boundaries of the individual firm to better exploit downstream and upstream linkages, reflecting the nature of the relationships between supply chain partners. Conversely, in the reviewed references cost modelling is treated as a separate problem from determining how the 'optimal' configuration of the PSC will look like. Activities such as cost attribution to products or cost estimation typically remain in the background as they are assumed to be preliminarily carried out. In the absence of additional insight on how these costs are derived, whether and to what extent the evaluation of cost may be recursively affected by the PSC model it contributes to optimise remain unclear.

Another economic aspect is demand estimation and modelling. With reference to healthcare systems the importance of detecting changes in demand patterns to ensure more responsive delivery has been presented [81,94]. However, the findings suggest that in framing a PSC model knowledge of demand is assumed to be available, either as a deterministic datum or as a stochastic function capable of generating it.

Finally, an emerging theme that is largely undetected in the examined literature is the 'end-of-life' stage within PSC. As pharmaceuticals products become more largely utilised, the routes of contamination through the food chain, and the challenges posed by new compounds to the treatment of wastewater become of greater concern (for example, [95]) and can only be detected by taking a 'circular' view on an economy. Only one of the retrieved references addresses medicines end-of-life aspects [96]. However, for its specialist approach and object of analysis it was deemed outside scope.

This leads to the following implications:

- From a theoretical perspective, the agnosticism of mathematical PSC models towards the characteristics of the underpinning manufacturing, service provision and information technologies characterising alternative PSC configurations will need to be addressed to ensure that the merits of alternative product or process technologies or business models are adequately compared.
- From a practical perspective, future PSC models should bridge the gap between modelling medicine manufacturing and distribution operations, and modelling the usage of pharmaceutical products downstream through healthcare service provision workflows.

5. Conclusions

The research presented in this paper was motivated by the debate on how best to evaluate the multifaceted aspects of PSC reconfigurations opportunities enabled by technology interventions in medicine manufacturing, as well as more patient-centric delivery models. To do so, a critical synthesis of the approaches commonly employed in the academic literature and industry practice was presented—to identify the relevant engineering–economic aspects of a PSC; to conceptualise those aspects through visualisation, and to evaluate them analytically. Synthesising arguments were obtained to address the following questions: "What is meant by PSC for modelling purposes?"; and "How is a PSC conceptualised through visualisation?"; "Which aspects of a PSC are expressed quantitatively, and how"?

The main contribution of this research is the application of a systems approach to OR problems, expanding on the seminal work of [15], to critically evaluate gaps between the characteristics of a PSC, which are currently modelled, and those that should be considered in a context where reconfigurations opportunities are being targeted. In the absence of a systems view of OR,

existing work tends to focus on the effectiveness and efficacy of model-solving activities, while overlooking potentially relevant aspects such as conceptual modelling, how a conceptual model informs the outline of a mathematical model, and which actions are eventually informed by the identified solution.

While application of critical interpretative synthesis is not new, to the authors' knowledge this is one of the first attempts to apply it to textual data expressed in mathematical rather than natural language. This application resulted in a major departure from existing reviews that enumerate and classify models based solely on the approach declared in the reviewed reference. Finally, this research distinguishes between models that refer to broader managerial problems concerning a PSC (for example, rank alternatives, or optimise a figure of merit), and models of the PSC itself, with a particular emphasis on its 'system' qualification. This distinction is in line with a shift in theory building, from emphasising supply chain *management*, to emphasising what is purportedly managed.

Most concepts and models of the PSC are misaligned with the view that a more patient-centric delivery solutions should be pursued. In principle, the most advocated position is that the PSC should be embedded in its broader ecosystem—namely, healthcare provision—most models draw their boundaries up to a point where a physical product reaches the shelves, regardless of whether and how effectively it is used to treat a condition. Based on the reviewed items, neither the definitions nor the models of the PSC available seem to reflect the theoretical view that more patient-centric delivery solution should be pursued.

While it is recognised that end-to-end benefits of future PSC require assessment of specific technology intervention, most models disclose little or no insight into the underpinning manufacturing technology being evaluated. This also applies to information and communication technologies, as most models do not provide insight into how the data which supposedly are needed to populate them are to be generated, stored, retrieved and transmitted. Finally, while operations research plays a prominent role in the formulation and solution of most PSC models, the achievement of a preliminarily understanding of the PSC through formalised supply chain mapping is either absent or poorly structured.

Economic aspects profoundly determine how an 'optimal' PSC configuration may look like. However, these aspects are largely treated as common knowledge rather than modelled in turn in such a way as to investigate whether, and to what extent, the evaluation of cost may be recursively affected by the PSC model it contributes to optimise.

This research has a series of limitations. Conclusions are drawn from a limited sample of the literature on the topic. Alternative combinations of search strategies and librarian resources may have led to a different sample. In addition, despite the authors' efforts to guarantee methodological rigour, an inherent element of subjectivity in shaping the synthesising argument could not be eliminated.

Currently, the quality of a model of the PSC in particular, and of a supply chain in general, seem to reside in its degree of sophistication and obscurity to the user. Achieving ambitious results such as reconciling conflicting environmental and economic objectives and making accurate predictions about the future appears more appealing than contributing to our understanding of a problem situation. Future research is needed to help inform the analyst's understanding of how value is delivered in use to the patient to attain beneficial outcomes, rather than chasing 'precision' while leaving the most relevant part of the problem outside the scope and boundaries of the analysis. From a methodological perspective, there are ample margins to develop better interfaces between conceptual and mathematical modelling, linking more systematically supply chain visualisation and mapping techniques to the identification and formulation of appropriate supply chain analytics. From a practical perspective, academics and practitioners should be able to navigate a growing, intricate landscape of approaches to PSC modelling with a more critical eye, rather than having to commit to specific tools and techniques a priori.

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Appendix A

Table A.1
Reviewed primary literature, system-related dimensions.

Reference	Context		Modelled phenomenon						Diagram			Boundaries			Scope							Relationships				
	COM	NPD	PIS	PRS	IDS	ITI	PDP	PBI	NNA	CEF	PSE	SIS	SUN	ECS	SCE	SIT	RES	ACT	CAM	PMT	PMA	MSC	DST	INF	TPR	ETR
[102]													*Excluded (saturation)*													
[82]	•		•						•				•			•		•		•		•				
[63]	•				•								•			•				•		•	•			
[103]	•				•								•			•						•	•			
[104]		•					•		•			•						•							•	
[70]	•				•				•				•			•					•		•			
[62]		•	•						•				•		•	•	•	•	•	•	•	•				
[105]													*Excluded (saturation)*													
[96]													*Excluded (out of scope)*													
[68]	•			•					•			•					•									
[69]		•					•					•			•			•		•					•	
[45]	•					•			•				•			•				•				•		
[46]	•		•										•			•								•		
[79]	•			•					•			•						•								•
[55]	•		•						•			•					•	•		•		•				
[66]	•			•								•					•	•							•	
[106]		•	•				•								•			•				•				
[42]		•			•								•			•						•				•
[71]	•	•		•			•		•			•			•		•				•	•			•	
[49]	•							•		•				•		•									•	
[107]	•			•							•	•						•	•	•		•				
[108]	•		•										•			•	•			•		•				
[51]		•	•						•				•		•	•		•		•		•			•	
[74]	•							•	•					•	•	•										•
[109]	•				•							•					•	•						•		•
[64]	•				•				•				•			•										•
[67]	•				•					•				•		•								•		
[59]	•				•							•					•					•				
[110]	•	•		•			•		•			•			•		•				•	•			•	
[111]	•				•							•														•
[75]	•				•				•				•			•							•			
[60]	•				•								•			•						•				
[112]		•					•					•						•							•	
[72]	•	•		•			•		•			•			•		•	•		•		•			•	
[113]													*Excluded (saturation)*													
[11]													*Excluded (out of scope)*													
[58]	•			•							•		•			•		•	•			•			•	
[53]	•							•	•				•			•										•

(*continued on next page*)

Table A.1 (*continued*)

Reference	Context		Modelled phenomenon						Diagram			Boundaries			Scope							Relationships				
	COM	NPD	PIS	PRS	IDS	ITI	PDP	PBI	NNA	CEF	PSE	SIS	SUN	ECS	SCE	SIT	RES	ACT	CAM	PMT	PMA	MSC	DST	INF	TPR	ETR
[114]													*Excluded (saturation)*													
[78]	•		•								•		•			•	•	•		•	•	•				
[50]	•							•		•				•		•									•	
[115]													*Excluded (saturation)*													
[76]	•							•	•					•				•						•		•
[116]		•					•		•						•	•				•					•	
[117]	•			•							•	•					•	•	•	•		•				
[57]	•			•							•	•					•	•		•		•				
[37]													*Excluded (out of scope)*													
[118]	•		•						•								•	•	•	•		•			•	
[47]	•					•			•				•			•								•		
[73]		•					•					•			•			•		•					•	
[91]	•			•					•				•				•	•		•		•				
[65]	•			•					•			•					•	•		•		•				
[85]	•		•						•				•			•	•	•		•		•				
[80]	•			•								•						•								•
[119]	•		•								•	•						•	•	•		•		•		
[120]		•					•		•			•					•	•		•					•	
[121]													*Excluded (saturation)*													
[61]		•	•				•		•			•			•		•	•		•		•			•	
[122]	•		•								•		•			•	•	•		•	•	•				
[123]	•				•								•			•				•		•				•
[77]	•							•	•					•				•						•		•
[39]	•				•							•					•	•						•		•
[124]	•				•				•				•			•						•				
[86]	•				•				•				•			•				•					•	
[48]													*Excluded (out of scope)*													
[125]	•				•							•					•	•						•		•
[126]	•				•				•				•			•						•	•			

COMM: Commercial Supply Chain (existing product); CLI/ NPD: Clinical Trial Supply Chain / New Product Development; PIS: Production-Inventory System; PRS: Production System; IDS: Inventory and Distribution System; ITI: Information Technology Infrastructure; PDP: Product development pipeline; PBI: Practice/Behaviour in Industry; NNA: non-formalised node-arc diagram; CEF: Cause/Effect (such as, causal loops; failure modes and effect); PSE: Process system engineering (such as recipe diagrams, State-Task-Network); SIS: Single site; SUN: Supply Network; ECS: Economy sector; SCE: Scenario; SIT: Site/Location, or organisation; RES: Resources (such as Equipment/Machinery, Production line, personnel); ACT: Activity/Task; CAM: Campaign; PMT: Products/Materials, by type; PMA: Product/Materials, by age; MSC: Materials supplier-customer; DST: distance; INF: Information Flows; TPR: Temporal precedence / cause-effect; ETR: Economic transactions.

Table A.2
Reviewed primary literature, manufacturing dimensions.

Reference	Geography	Product life-cycle stages									Pharmaceutical product technology					Manufacturing technology			Real-word implemented
		PDV	STM	PRM	SEM	PCK	TRN	DIST	USE	WST	SDF	LDF	INJ	ONC	VAC	BAT	CNT	DIG	
[102]										*Excluded (saturation)*									
[82]	EU			•			•			•						•	•		
[63]	n.s.				•			•	•	•				•				•	
[103]	EU							•											
[104]	n.s.	•																	
[70]	n.s.				•			•	•					•					
[62]	US, EU			•	•	•	•		•	•						•			
[105]										*Excluded (saturation)*									
[96]										*Excluded (out of scope)*									
[68]	India				•	•													
[69]	n.s.	•																	
[45]	EU																	•	
[46]	EU																	•	
[79]	n.s.																		
[55]	India				•	•					•	•	•						•
[66]	EU				•							•	•			•			
[106]	n.s.	•			•					•									
[42]	US, EU, RU	•					•	•											
[71]	n.s.	•		•						•									
[49]	n.s.							•											
[107]	n.s.			•												•			
[108]	US			•	•	•		•											•
[51]	n.s.			•	•	•		•		•									
[74]	n.s.	•		•	•			•											
[109]	EU							•											
[64]	India							•											
[67]	n.s.				•			•		•								•	
[59]	n.s.							•											
[110]	n.s.	•		•						•									
[111]	n.s.							•											
[75]	EU						•	•											
[60]	n.s.				•		•			•									
[112]	n.s.	•																	
[72]	n.s.	•		•															
[113]										*Excluded (saturation)*									
[11]										*Excluded (out of scope)*									
[58]	n.s.			•			•										•		
[53]	US, Asia							•											

(*continued on next page*)

Table A.2 (*continued*)

Reference	Geography	Product life-cycle stages									Pharmaceutical product technology					Manufacturing technology			Real-word implemented
		PDV	STM	PRM	SEM	PCK	TRN	DIST	USE	WST	SDF	LDF	INJ	ONC	VAC	BAT	CNT	DIG	
[114]										*Excluded (saturation)*									
[78]	n.s.		•	•	•	•				•						•			
[50]	India							•		•									
[115]										*Excluded (saturation)*									
[76]	US							•											
[116]	n.s.	•																	
[117]	n.s.			•												•			
[57]	n.s.		•	•												•			
[37]										*Excluded (out of scope)*									
[118]	n.s.			•												•			
[47]	n.s.							•										•	
[73]	n.s.	•																	
[91]	EU		•	•	•	•					•								
[65]	EU			•															
[85]	n.s.			•	•		•												
[80]	India, EU				•						•		•						
[119]	EU				•						•					•			
[120]	n.s.	•																	
[121]										*Excluded (saturation)*									
[61]	n.s.	•			•												•		
[122]	n.s.		•	•	•	•				•						•			
[123]	US							•											
[77]	US							•											
[39]	n.s.							•											
[124]	UK							•		•									
[86]	Africa							•							•				
[48]										*Excluded (out of scope)*									
[125]	n.s.							•											
[126]	China						•	•											

PDV: Product development; STM: Starting materials manufacture; PRM: Primary manufacturing (Active pharmaceutical ingredients); SEM: Secondary manufacturing (dosage forms); PCK: Product packaging; TRD: Transport; DST: distribution (wholesale/dispensing pharmacies); USE: medicine utilisation; WST: waste medicine disposal; NS: not specified; SDF: Solid dosage form; LDF: Liquid dosage form; INJ: Injection; ONC: Oncology; VAC: Vaccines; BAT: Batch; CNT: Continuous; DIG: Digital information technologies.

Table A.3
Reviewed primary literature, mathematical modelling dimensions.

Reference	Mathematical model																		Solution				
	Classification	Matrices (definitions in Fig. 2 and Table 2)											Tech depend formal			Temp depend formal			Approach to Uncertainty		COP	SIM	AHC	ALG	SUJ
		V	V_e	U	U_p	U_c	U_e	s	d	b	f	tau	FXT	CBR	None	INT	LAG	None	DET	PRB					
[102]													*Excluded (saturation)*												
[82]	Archetype I	•		•	•	•		•	•	•	•	•		•		•				•	•				
[63]	Archetype I	•						•	•	•	•		•					•		•				•	
[103]	Archetype I	•				•		•	•	•	•		•			•			•					•	
[104]	Archetype III														•			•		•		•	•		
[70]	Archetype III														•			•	•		•				
[62]	Archetype I	•						•	•	•	•	•					•			•	•	•			
[105]													*Excluded (saturation)*												
[96]													*Excluded (out of scope)*												
[68]	Archetype II														•			•	•					•	•
[69]	Archetype III					•						•					•			•	•				
[45]	Archetype II															•		•	•				•		
[46]	N/A																								
[79]	N/A																								
[55]	Archetype I	•		•	•	•		•	•	•	•		•	•		•		•	•		•				
[66]	Archetype II											•	•		•	•				•	•	•			
[106]	Archetype I	•						•	•	•	•				•	•				•	•	•			
[42]	Archetype I	•						•	•						•			•		•	•	•			
[71]	Archetype I	•		•	•	•		•	•	•	•	•		•		•				•	•				
[49]	Hybrid/BB																								•
[107]	Archetype I	•		•	•			•	•			•	•	•				•	•						
[108]	Archetype I	•		•		•		•	•	•	•		•	•		•			•		•				
[51]	Archetype I	•		•				•	•	•	•	•	•	•			•			•	•	•			
[74]	Hybrid/BB																			•		•			
[109]	Archetype I	•						•	•						•			•		•	•	•			
[64]	Archetype II												•			•			•		•				
[67]	Archetype II																								•
[59]	Archetype I	•		•				•	•	•	•	•	•			•			•				•		
[110]	Archetype I	•		•	•	•		•	•	•	•	•		•		•				•	•				
[111]	Archetype II																			•		•	•		
[75]	Hybrid/BB																			•	•	•	•		
[60]	Archetype III	•		•				•	•						•			•		•	•	•			
[112]	Archetype III					•						•					•			•	•				
[72]	Archetype III	•		•	•	•		•	•				•	•		•				•	•				
[113]													*Excluded (saturation)*												
[11]													*Excluded (out of scope)*												
[58]	Archetype I	•		•	•			•	•			•						•	•		•				
[53]	Archetype I	•						•	•									•	•					•	

(*continued on next page*)

Table A.3 (*continued*)

Reference	Mathematical model																				Solution				
	Classification	Matrices (definitions in Fig. 2 and Table 2)											Tech depend formal			Temp depend formal			Approach to Uncertainty		COP	SIM	AHC	ALG	SUJ
		V	V_e	U	U_p	U_c	U_e	s	d	b	f	tau	FXT	CBR	None	INT	LAG	None	DET	PRB					
[114]													*Excluded (saturation)*												
[78]	Archetype I	•		•	•			•	•	•	•	•		•			•		•		•				
[50]	Hybrid/BB														•										•
[115]													*Excluded (out of scope)*												
[76]	N/A																								
[116]	Hybrid/BB														•					•			•		
[117]	Hybrid/BB																		•		•				
[57]	Archetype I	•	•	•	•		•		•				•	•				•	•					•	
[37]													*Excluded (out of scope)*												
[118]	Archetype I	•		•		•		•	•	•	•	•		•		•			•		•		•		
[47]	N/A																								
[73]	Archetype III					•						•					•			•	•				
[91]	Hybrid/BB												•					•	•					•	
[65]	Archetype II																	•	•		•				
[85]	Archetype I	•		•		•		•	•	•	•			•		•			•		•				
[80]	Archetype II														•			•	•						•
[119]	Hybrid/BB												•					•	•			•			•
[120]	Archetype III					•						•			•		•			•	•	•			
[121]													*Excluded (out of scope)*												
[61]	Archetype III	•				•		•	•	•	•	•					•			•	•				
[122]	Archetype I	•		•	•			•	•	•	•	•		•			•		•		•				
[123]	Archetype I	•		•				•	•									•			•				
[77]	N/A																								
[39]	Archetype I	•						•	•						•			•		•	•				
[124]	N/A																								
[86]	Archetype II																	•	•						•
[48]													*Excluded (out of scope)*												
[125]	Archetype I	•						•	•						•			•		•	•				
[126]	Archetype I														•			•	•						

N/A: not applicable (e.g., conceptual or case study); FXT: Fixed topology; CBR: Cookbook recipe/technical coefficient given; INT: Inter-temporal (consecutive time slices); LAG: time-lagged (non-consecutive time slices); DET: Deterministic; PRB: Probabilistic; COP: Constrained optimisation (include data envelopment analysis, and curve-fitting e.g., least squares); SIM: Simulation; AHC: Artificial intelligence/Heuristics/Classification algorithm; ALG: Algebraic, closed form; SUJ: Subjective judgment e.g., scoring system.

Appendix B

Table B.1. Evaluation of selected definitions of pharmaceutical supply chain, and generic supply chain according to the rules of formal conceptual definition.

Definitions' references	Criteria*						
	The term defined can be replaced by the words used to define it in a sentence and not have the sentence change meaning (Replacement)	*The concept is distinguished from seemingly similar concepts by excluding shared terms* (Denotation matches connotation)	*Ambiguity is reduced by avoiding terms such as "and, or, and/or", and by adding modifiers* (Clarity)	*As few terms as possible are used to convey the concept* (Parsimony)	*An existing definition is replaced only after ascertaining that a new definition would be superior* (Consistency)	*An existing definition is not unnecessarily made less precise by expansion*	*The concept is defined without introducing new hypotheses*
Pharmaceutical							
Proposition 1	√	√	√	√	√	√	√
Existing definitions							
[104]	✗ (1)	✗ (2)	√	√	N/A (3)	N/A (3)	√
[70]	✗ (1)	√ (4)	√	√	N/A (3)	N/A (3)	√
[62]	✗ (1)	√	√	√	N/A (3)	N/A (3)	√
[105]	√	√	√	√	N/A (3)	N/A (3)	√
[68]	√	√	✗(5)	✗(5)	N/A (3)	N/A (3)	√
[45]	√	√	√	√	N/A (3)	N/A (3)	√
[43]	√	✗ (2)	✗(5)	✗(5)	N/A (3)	N/A (3)	✗ (7)
[42]	✗ (1)	✗ (2)	√	✗(5)	N/A (3)	N/A (3)	✗ (7)
[11]	√	√	√	√	N/A (3)	N/A (3)	✗ (7)
[51]	√	√	√	√	N/A (3)	N/A (3)	√
[74]	✗ (1)	√	√	✗(5)	N/A (3)	N/A (3)	√
[64]	✗	√	√	√	N/A (3)	N/A (3)	√
[35]	√	√	√	√	√	√	√
[110]	✗	✗ (6)	√	√	N/A (3)	N/A (3)	√
[111]	√	✗ (2)	✗(5)	✗(5)	√	✗(5)	√
[113]	√	✗ (2)	✗(5)	✗(5)	N/A (3)	N/A (3)	√
[76]	✗	√	✗(5)	✗(5)	√	√	√
[37]	✗	✗ (2)	✗ (2)	√	√	√	✗ (7)
[118]	✗	√	√	√	N/A (3)	N/A (3)	√
[90]	✗	√	√	√	N/A (3)	N/A (3)	√
[91]	✗ (1)	✗ (2)	√	√	N/A (3)	N/A (3)	√
[85]	✗	√	√	✗(5)	N/A (3)	N/A (3)	✗ (7)
[61]	✗ (1)	√	√	√	N/A (3)	N/A (3)	√
[121]	✗ (1)	√	√	✗(5)	N/A (3)	N/A (3)	√
[122]	✗ (1)	✗ (2)	√	√	N/A (3)	N/A (3)	√
[77]	√	√	√	√	N/A (3)	N/A (3)	√
[39]	√	√	√	✗(5)	√	✗(5)	√
[97]	√	√	√	√	N/A (3)	N/A (3)	√
[125]	√	√	√	√	N/A (3)	N/A (3)	√
Generic supply chain							
Review papers							
[34]	√	√	√	√	N/A (3)	N/A (3)	√
[99]	√	√	√	√	N/A (3)	N/A (3)	√
[38]	✗	√	√	√	√	√	✗ (7)
[31]	√	√	√	√	N/A (3)	N/A (3)	√
[41]	✗	√	✗	✗(5)	N/A (3)	N/A (3)	√
[54]	√	√	√	√	N/A (3)	N/A (3)	√
Textbooks							
[20]	√	√	√	√	N/A (3)	N/A (3)	√
[127]	✗	✗	√	✗(5)	N/A (3)	N/A (3)	✗ (7)

Notes:

* Adapted from the rules of good conceptual definition (Wacker, 2004). One of the original rules has been omitted here since none of the examined works deals with the empirical testing of the concept of pharmaceutical supply chain; [1]Definition is not given specifically (E.g. does not read like: "The PSC is …"), and may not be presented in a consequential manner; [2]Adjacent concepts coexist; [3]No reference to existing conceptual definitions is made; [4]Focus on a specific medical supply; [5]Qualifications keep being added; [6]Generic concepts used instead of specific concept of pharmaceutical supply chain; [7]Hypotheses embedded in definition (for example, cost-effective). N/A: not applicable.

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